UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,547	10/17/2001	Jim Wells	SUNESIS.002DV1	8070

20995 7590 07/10/2003

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	13

DATE MAILED: 07/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/981,547	Applicant(s) WELLS ET AL.	
File Copy	Examiner Jon D Epperson	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,59 and 61-66* is/are pending in the application.

4a) Of the above claim(s) *62-64 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58,59,61 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

1. The Response filed April 18, 2003 (Paper No. 10) is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 40-80 were pending in this application. The Examiner withdrew claims 40-57, 62-64 and 66-80 in Paper No. 9 as being drawn to non-elected inventions. Applicants canceled claims 40-57, 60 and 67-80 in Paper No. 10. Therefore, claims 58-59, 61 and 65 are examined on the merits in this Action.

Election/Restriction

4. In response to the restated Restriction and Election of Species requirement, Applicants reaffirm the election of the invention of Group IV (58-66), with traverse. Applicants further reaffirm their election of species requirement, also with traverse for the reasons of Record i.e., in Paper No. 8 (see Papers No. 10, page 3, paragraphs 2-5).

5. In response the Examiner reaffirms the reasons why these arguments were not found persuasive (i.e., see Paper No. 9, paragraphs 7-17, which are incorporated in their entirety herein by reference).

6. Because Applicants did not add any new arguments to the record the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

IDS

7. The IDS references number 16 and 20 have been considered by the Examiner.

Withdrawn Objections/Rejections

8. The objection to the specification is hereby withdrawn in view of applicant's amendments thereto. The rejection under the first paragraph of 35 U.S.C. 112 denoted "New Matter" is hereby withdrawn in view of Applicants' arguments and cancellation of claim 60. The rejection under 35 U.S.C. 102(b) by Erlanson et al is hereby withdrawn in view of Applicants' arguments and/or cancellation of claims. The Double Patenting Rejections are hereby withdrawn in view of Applicants' submission of a Terminal Disclaimer (see below) in Paper No. 12. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

9. Claims 58-61 and 65 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claim 58 outlines method steps for identifying a "ligand" that binds to a "site of interest" on a "target protein" wherein said ligand covalently binds to said target protein via a "chemically reactive group", wherein no structural features or identifying characteristics are provided for the "ligands", "chemically reactive groups" or "target proteins" and no guidance is provided for determining where the "site of interest" might reside on said target proteins. The scope of this claim includes an infinite number of methods for identifying an "infinite" number of possible ligands that would bind to an "infinite" number of potential sites on an "infinite" number of proteins that have not been "specifically" disclosed by Applicants. Furthermore, the specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the "ligands" or the "chemically reactive groups" and likewise no structural or identifying features has been set forth for the "target proteins." In addition, the specification and claims do not provide ***any*** guidance as to where these "sites of interest" might reside on these undisclosed target proteins. Consequently, it is not possible to determine *a priori* which "ligands", "chemically reactive groups", "target proteins" and "sites of interest" would be

encompassed by the present claims because there is no commonality that can link together ***all*** of these unknown variables i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* what "ligands", "chemically reactive groups", "target proteins" and "sites of interest" should be included in this genus from the absence of working examples provided by applicants.

With respect to adequate disclosure Applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* that provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat*_(CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Here, Applicants claims are broad in scope and of an unpredictable nature (see above). Consequently, the Examiner contends that the specification fails to provide adequate disclosure because Applicants have disclosed only ONE example (see specification, page 24, outlining the use of a "thymydilate synthase" target modified with a "cysteamine" linker for screening "aldehyde" ligands wherein the side of interest is the "active site" of the protein), which would not teach a genus that would encompass virtually an unlimited number of proteins, ligands (in a broad range of classes i.e., both inorganic and organic) and linkers.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, ***not general***, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, simply reciting a "laundry list" of potential ligands, chemically reactive groups and target proteins (e.g., see specification, page 8, last paragraph, wherein target protein may be "enzymes, such as proteases and thymidylate synthease, steroid receptors, nuclear proteins, allosteric enzyme inhibitors, clotting factors ... etc.") is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicants were not in possession of the claimed genus.

Response

10. Applicant's arguments directed to the above Written Description rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues that **[1]** the present invention is not directed to target proteins or ligands (i.e., the target protein(s) and ligand(s) are "not critical" to the invention) but rather concerns "broadly applicable screening methods" using mass spectrometry to analyze protein tethered ligands. Applicants further state that the method is not limited to any particular protein structure,

any particular ligand and that the ligand may be linked covalently to the protein through any type of covalent bond (i.e., any type of linker) and, as a result, Applicants do not need to provide a written description for these "non-critical" elements (see Paper No. 10, pages 7-8, see especially page 9, last paragraph, "As discussed above, the disclosure of specific protein or ligand structures is not needed for adequate written description"). Furthermore, even if these "non-critical" elements need to be adequately described the specification and general skill in the art would suffice (see Paper No. 10, pages 7-8; see also pages 9-10), **[2]** "[t]he Examiner has given no reason why one skilled in the art would not reasonably accept that the screening method of the invention can be performed with any target protein and any ligand, capable of forming any type of covalent bond, i.e., that applicants were in possession of the claimed invention" (see Paper No. 10, page 9), **[3]** "[i]t is hard to imagine how else Applicants could provide guidance in the specification but by providing an extensive listing of exemplary embodiments within the scope of invention" (see Paper No. 10, page 10, paragraph 5).

This is not found persuasive for the following reasons:

The Examiner contends that **[1]** that the target protein(s), ligand(s) and linker(s) are critical to the invention because the claimed "tethering" method could not be performed without them. If Applicants do not have possession of all the claimed target protein(s), ligand(s) and linker(s) then Applicants do not have possession of all the methods for using said protein(s), ligand(s) and linker(s). Here, Applicants have admitted that their screening method is broad in scope (see Paper No. 10, page 8, "broadly applicable screening method") and could employ *any* protein, ligand and linker (i.e., Applicants claims read on an infinite number of possibilities).

Therefore, Applicants must provide an adequate written description for these claimed "essential" materials and their method of use within the "full scope" of the claimed invention.

The Examiner further contends that Applicants must set forth a "representative number of examples" that would allow a person of skill in the art to determine that Applicants had possession of the full scope of the claimed invention (i.e., adequate written description). With respect to adequate disclosure of the scope of the presently claimed generic Applicants are referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* that provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

The Examiner further argues that the holding in *University of California v. Eli Lilly and Co.* (cited above) would apply to methods (not just products) because virtually any compound claim could be transformed into a method claim simply by rewording the claim in terms of a method of using the compound (i.e., the protein, ligand and/or linker). In this case, the claimed method *depends* upon the finding that a ligand has the ability to covalently bind to a site of interest on a target protein using an appropriate linker (i.e., become tethered at or near a site of

interest). Without such a compound, it is impossible to practice the claimed method. It means little to "invent" a method if one does not have possession of all the essential ingredients that are required to practice said method. Without all of the claimed protein(s), ligand(s) and linker(s), the claimed invention is more theoretical than real.

Here, Applicants argue that a "single working example" (see specification, page 24, outlining the use of a "thymydilate synthase" target modified with a "cysteamine" linker for screening "aldehyde" ligands wherein the side of interest is the "active site" of the protein) would allow a person of skill in the art to determine that they were in possession of an "infinite" number of methods using an "infinite" number of unrelated proteins, ligands and linkers. The Examiner contends that ONE working example is not "representative" of such broad scope (see rejection above). In addition, as stated in the original rejection, the general knowledge and level of skill in the art do not supplement the omitted description because specific, ***not general***, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is ***enormous*** and ***highly variant***, simply reciting a "laundry list" of potential ligands, chemically reactive groups and target proteins (e.g., see specification, page 8, last paragraph, wherein target protein may be "enzymes, such as proteases and thymidylate synthease, steroid receptors, nuclear proteins, allosteric enzyme inhibitors, clotting factors ... etc.") is insufficient to teach the entire genus. Furthermore, the Examiner contends that the art is inherently unpredictable because the genus is enormous and highly variant and thus would require even a greater number of examples than an invention narrowly constrained to predictable class of compounds.

The Examiner contends **[2]** that Applicants have not provided a "representative" number of Examples that would allow a person of skill in the art to determine that they were in possession of the claimed invention (see above). Furthermore, the Examiner contends that the Art is inherently unpredictable (see below) and would require an even greater showing of "representative" examples than a more predictable art area.

Applicants requested that the Examiner "provide specific scientific reasoning why one skilled in the art would not accept that at the effective filing date of the present application applicants were in the possession of the invention" (see Paper No. 10, page 9). As requested, the Examiner sets forth a new reference (see Delano, W. L. "Unraveling hot spots in binding interfaces: progress and challenges" *Current Opinion in Structural Biology* **2002**, *12*, 14-20) for the sole purpose of adhering to Applicants' request. However, please note that the Examiner does not believe that such a reference is necessary because as stated above (and also in the original rejection) Applicants disclosure of only "one working example" is not "representative" of such broad scope.

Delano (see entire document) outlines some of the challenges faced by today's researchers that are trying to analyze "hot spots" in protein-binding interfaces (e.g., proteins that bind to other proteins and/or other ligands). The reference explicitly cites Applicants claimed invention (see Reference 47-48 therein) and thus is a particularly relevant reference (i.e., the reference represents analogous art). Delano states that "there are no general patterns of hydrophobicity, shape or charge that can be used as a basis for predicting which protein atoms will participate in hot spots" (see Delano, page 14, column 1, paragraph 2) and defines said hot spots as "a residue that, when mutated to alanine, gives rise to a distinct drop in the binding

constant (typically tenfold or higher) [of a protein and/or another ligand]" (see Delano, page 14, column 2, paragraph 2; please note that this technique is called "alanine scanning"). Delano goes on to further define potential destabilizing perturbations that occur as a result of these "alanine mutations" in protein-ligand interactions as "(a) loss of optimal van der Waals contacts; (b) loss of electrostatic pairings ... and (i) global unfolding" (see Delano, page 16, figure 3).

Here, the Examiner contends that Applicants claimed method requires "mutations" in the target protein (i.e., to equip the protein with a chemically active group at or near a site of interest which facilitates covalent bonding to the ligand) that would prevent said target protein from binding to its ligand(s) just as the "alanine mutations" interfered with the protein-protein and/or protein-ligand interactions in Delano via "(a) loss of optimal van der Waals contacts; (b) loss of electrostatic pairings ... and (i) global unfolding" (see Delano, page 16, figure 3). Consequently, the Examiner contends that Applicants are not in possession of the full scope of the claimed invention because Delano states that "there are no general patterns of hydrophobicity, shape or charge that can be used as a basis for predicting which protein atoms will participate in hot spots [i.e., which protein atoms when mutated will destabilized the protein and/or prevent ligand binding]" (see Delano, page 14, column 1, paragraph 2) and, as a result, Applicants would not be able to determine *a priori* whether their required "mutations" would or would not destabilize, unfold and/or prevent their target proteins from covalently bonding to their respective ligands at a site of interest. Just because Applicants have shown that a thymydilate synthase can be "mutated" with a cysteamine and still retain its ability to bind to a ligand does not mean that all proteins, ligands and linkers will act in a similar manner. Furthermore, given the specificity and fragile nature of protein-ligand interactions and the myriad of mechanisms by which a simple

seeming innocuous mutation can unpredictably destabilize and/or prevent ligand binding, the Examiner contends that the majority of Applicants claimed embodiments would be inoperative (see Delano, figure 3 which outlines just how unpredictable the effects of protein mutations can be, "In particular, changes in interface dynamics are very hard to demonstrate or rule out experimentally because of the limitations of available technology. These effects, which relate to the plasticity of protein interfaces, account for much of the current uncertainty in the interpretation of alanine scanning data [i.e., what happens to the stability of a protein when it is mutated as is the case here]").

Finally, the Examiner contends **[3]** that Applicants should not be afforded greater protection under the law then they are actually entitled to just because their invention is inherently difficult to adequately describe.

Accordingly, the Written Description rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

11. Claims 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**) and Ganem et al (Ganem, B.; Li, Y. T.; Henion, J. D. "Detection of noncovalent receptor-ligand complexes by mass spectrometry" *Journal of the American Chemical Society* **1991**, 113(16), 6294-6).

For **claims 58**, Pitner et al (see entire document) teaches [a] a method for identifying a ligand less than 2000 daltons in size (see Pitner et al, figures 6-7, see also

column 4, paragraph 5, see also Examples 1-9, showing PC ligands that are ~250 Da), [b] that bind to a chemically reactive group (see Pitner et al, figure 1, showing chemically reactive group could be either SH or NH, see also column 3 lines 49-58), [c] at a site of interest on the target protein (see Pitner et al, figure 1, disclosing the "antigen binding site" as the "target of interest", see also column 3, paragraph 1), [d] to form a target protein-ligand conjugate (see Pitner et al, figure 1, see also figures 6-7, see also Examples 1-9).

For **claims 59-61**, Pitner et al discloses PC ligands that are ~250 Da (see Pitner et al, entire document, especially figures 1, 6-7 and Examples 1-12).

The prior art teachings of Pitner et al differ from the claimed invention as follows:

For **claims 58**, Pitner et al is deficient in that it does not specifically teach the use of "mass spectrometry" for detecting the protein-ligand conjugate. Pitner et al would require the "identification" of "modified" antigens like PC-MAL that possess a stronger binding affinity to antibodies like SH-McPC603 than the normal PC ligand (see Pitner et al, figures 3 and 7) using an analytical technique like mass spectrometry.

However, Ganem et al teaches the following limitations that Pitner et al lacks:

For **claim 58**, Ganem et al teaches the use of mass spectroscopy for "identifying enzyme-substrate, receptor-ligand, and antibody-antigen complexes" (see Ganem et al, page 6294, paragraph 1; see also, page 6295, second column, last paragraph. Furthermore, Ganem et al teaches that the ligand can be "identified" using mass spectrometry (see Ganem et al, page 6296, "This result indicates that noncovalently

bound species can be detected directly in a complex mixture without chromatographic separation").

Please note that Ganem teaches both "covalent" and "non-covalent" interactions and explicitly states that it can be used for antibody-antigen complexes like the ones used in Pitner et al (see Ganem et al, page 6294, paragraph 1). For example, Ganem et al discloses a peak at 1803.1 for the "non-covalent" complex of $(FKBP + FK506 + 7H)^{7+}$ and also another peak at 1969.8 for the uncomplexed FKBP $(FKBP + 6H)^{6+}$ (see Ganem et al, page 6295, figure 4). The 1803.1 peak clearly demonstrates that mass spectroscopy can be used to identify "non-covalent" complexes because the 1803.1 peak represents the molecular weight of FKBP complexed non-covalently to FK506. However, the spectrum further shows a peak at 1969.8 for the un-complexed FKBP, which contains many "covalent" bonds (e.g., FKBP is a small hydrophilic protein which has many "covalent" bonds such as the covalent bonds that connect the peptide backbone or the amino acid side chains). Consequently, it would be immediately obvious to a person of skill in the art that "covalent" bonds do NOT interfere with the experiment (i.e., the fact that FKBP has "covalent" bonds does not render it undetectable in a mass spectrometer). In fact, if the mass spectrometer could not detect "covalent" bonds then the mass spectrometer would not provide the signals shown in figure 4 of Ganem because both the FKBP and the FK506 have "covalent" bonds. Therefore, it would be immediately obvious to one of ordinary skill in the art that the mass spectrometer could be used to detect both "covalent" and "non-covalent" antibody-antigen interactions.

It would have been obvious to one skilled in the art at the time the invention was made to "identify" a "ligand" that binds to a "target protein" wherein said "ligand" possesses a "chemically reactive group" and covalently binds to said "target protein" wherein said ligand is less than 2000 daltons as taught by Pitner et al in conjunction with the mass spectrometer techniques as taught by Ganem et al because Ganem et al explicitly states that the mass spectrometry "can be applied to problems of biological interest [including] ... proteins" and that the methods are good for "detecting and identifying enzyme-substrate, receptor-ligand, and ***antibody-antigen complexes***", (see Ganem et al, page 6294, paragraph 1), which would encompass the "antibody-antigen" complexes of Pitner et al. Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Ganem et al with the ligand-receptors as taught by the teachings of Pitner et al because Ganem et al explicitly states that the "ion-spray MS can be performed in water without cosolvent, which is ideal for most biological systems. Multiple charging produces a family of molecular ions and dramatically reduces the mass-to-charge ratio so that even quadrupole mass spectrometers having a typical range of 1000-2000 daltons (DA) can determine high MW species with unit mass resolution" (see Ganem et al, page 6294, second paragraph) (see also Ganem et al, page 6296, last paragraph).

Furthermore, one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Ganem et al with the "antibody-antigen" complexes as described by Pitner et al because Ganem et al discloses that BOTH "covalent" and "non-covalent" interactions can be measured using a mass spectrometer (see below). In order

for the method of Pitner et al to work the modified antibodies must bind "covalently" to their respective antigens (see Pitner et al, figure 1 disclosing the covalent attachment of an antigen to a sulfhdryl group on the modified antibody). Therefore, any analytical technique that can confirm the "covalent" attachment of the antigen to the modified antibody is particularly useful. Consequently, a person of skill in the art would be motivated to "identify" even a known ligand using a mass spectrometer to determine the type of interaction (i.e., covalent v. non-covalent) to ascertain whether the modified antibody is truly able to bind to its respective antigen via a "covalent" bond as required by the method (as opposed to an induced conformational change in the antibody that might increase the normal antibody-antigen binding interactions via a "non-covalent" interaction). Furthermore, a person of skill in the art would be motivated to search for the modified antigens as disclosed by Pitner et al (e.g., PC-MAL, see figure 3) with mass spectroscopy as disclosed by Ganem et al to find modified antigens that can covalently bind to the antibodies.

Finally, one of ordinary skill in the art would have reasonably expected to be successful because Ganem et al shows a successful example of a protein-ligand interaction (e.g., between FKBP and FK506, see figure 4) and the antibody-antigen complexes disclosed by Pitner et al represent protein-ligand interactions. Furthermore, the reference explicitly states that it can be successfully applied to antibody-antigen interactions (see Ganem et al, page 6294, paragraph 1).

Response

12. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue **[1]** that "[s]ince antibodies are raised against antigens, the antigen of any particular antibody is, by definition, known. Accordingly, one reading the disclosure of Pitner et al. would not be motivated to search for any method for identifying the antigens present in the antigen-antibody complexes, given the fact that the antigens are known" (see Paper No. 10, page 11, paragraph 4), **[2]** Furthermore, Pitner et al. disclose a covalent bond between an antibody and an antigen, while Ganem et al. deal with the detection of non-covalent complexes. Therefore, one reading the disclosure of Pitner et al., even if for some reason the identification of the (already known) antigen were desirable, would not turn to Ganem et al., addressing a completely different problem (see Paper No. 10, page 11, paragraph 5), **[3]** the combined references would not make obvious the claimed invention i.e., the use of mass spectrometry to detect the formation of a covalent target protein-ligand conjugate (see Paper No. 10, page 11, paragraph, 6).

This is not found persuasive for the following reasons:

The Examiner contends **[1]** a person of skill in the art would be properly motivated to combine the Pitner et al and Ganem et al references because (as stated in the original rejection) Ganem et al explicitly states that mass spectrometry "can be applied to problems of biological interest [including] ... proteins" and that the methods are good for "detecting and identifying

enzyme-substrate, receptor-ligand, and *antibody-antigen* complexes" which would encompass the "antibody-antigen" complexes disclosed by Pitner et al (see Ganem et al, page 6294, paragraph 1).

Furthermore, Ganem et al explicitly states that the "ion-spray MS can be performed in water without cosolvent, which is ideal for most biological systems. Multiple charging produces a family of molecular ions and dramatically reduces the mass-to-charge ratio so that even quadrupole mass spectrometers having a typical range of 1000-2000 daltons (DA) can determine high MW species with unit mass resolution" (see Ganem et al, page 6294, second paragraph) (see also Ganem et al, page 6296, last paragraph). Please note that Applicants did not address this issue in Paper No. 10.

Furthermore, one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Ganem et al with the "antibody-antigen" complexes as described by Pitner et al because Ganem et al discloses that BOTH "covalent" and "non-covalent" interactions can be measured using a mass spectrometer (see below). In order for the method of Pitner et al to work the modified antibodies must bind "covalently" to their respective antigens (see Pitner et al, figure 1 disclosing the covalent attachment of an antigen to a sulfhdryl group on the modified antibody). Therefore, any analytical technique that can confirm the "covalent" attachment of the antigen to the modified antibody is particularly useful. Consequently, a person of skill in the art would be motivated to "identify" even a known ligand using a mass spectrometer to determine the type of interaction (i.e., covalent v. non-covalent) to ascertain whether the modified antibody is truly able to bind to its respective antigen via a "covalent" bond as required by the method (as opposed to an induced conformational change in the antibody that might increase the normal

antibody-antigen binding interactions via a "non-covalent" interaction). Please note that "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention", see MPEP § 2144").

Furthermore, the Examiner does not agree that all of the antigens are "known" and, as a result, do not need to be identified (see Paper No. 10, page 11, paragraph 11). For example, the antigen PC-MAL was synthesized (see Figure 3) and, as a result, was NOT known to be an antigen for the McPC603 antibody. It was "predicted" to have similar binding properties to PC based on a similar core structure, but it was NOT known. PC-MAL (see Pitner, figure 7) has to first be "identified" using a suitable analytical technique (such as mass spectroscopy) before it can be classified as a "known" antigen ***i.e., there is motivation to search for modified antigens that will bind to the antibody using mass spectrometry***.

The Examiner also contends **[2]** that Ganem et al does NOT teach exclusively "non-covalent" interactions as alluded to by Applicants and is NOT addressing a "completely different problem" (see Paper No. 10, page 11, paragraph 5). Ganem teaches both "covalent" and "non-covalent" interactions and explicitly states that it can be used for antibody-antigen complexes like the ones used in Pitner et al (see Ganem et al, page 6294, paragraph 1). For example, Ganem et al discloses a peak at 1803.1 for the "non-covalent" complex of (FKBP + FK506 + 7H)$^{7+}$ and also another peak at 1969.8 for the un-complexed FKBP (FKBP + 6H)$^{6+}$ (see Ganem et al, page 6295, figure 4). The 1803.1 peak clearly demonstrates that mass spectroscopy can be used to identify "non-covalent" complexes because the 1803.1 peak represents the molecular weight of FKBP complexed non-covalently to FK506. However, the spectrum further shows a peak at 1969.8 for the un-complexed FKBP, which contains many "covalent" bonds (e.g., FKBP

is a small hydrophilic protein which has many "covalent" bonds such as the covalent bonds that connect the peptide backbone or the amino acid side chains). Consequently, it would be immediately obvious to a person of skill in the art that "covalent" bonds do NOT interfere with experiment (i.e., the fact that FKBP has "covalent" bonds does not render it undetectable in a mass spectrometer). In fact, if the mass spectrometer could not detect "covalent" bonds as purported by Applicants then the mass spectrometer would not provide the signals shown in figure 4 of Ganem et al because both the FKBP and the FK506 have "covalent" bonds. Therefore, Ganem et al do not teach a "completely different problem" than Pitner et al as purported by Applicants because the physical distinction between "covalent" and "non-covalent" interactions as applied to mass spectroscopy is of no practical consequence. A person of skill in the art would have been motivated to combine Pitner et al with Ganem et al because Ganem et al explicitly states that mass spectrometry can be used for antibody-antigen complexes like the ones disclosed by Pitner et al (see Ganem et al, page 6294, paragraph 1) whether they are of a "covalent" nature or not.

Furthermore, as stated above a person of skill in the art would be motivated to use mass spectroscopy precisely because it does detect BOTH "covalent" and "non-covalent" bonds and, as a result, could help distinguish between modified antibodies that are binding to their antigens via the desired "covalent" bonds versus any unwanted "non-covalent" interactions that might occur through conformational changes to the antibody upon modification (e.g., with a sulfhydryl group).

Finally, the Examiner contends **[3]** that the combined references do teach the claimed invention because Pitner et al discloses a "covalent" complex between a target protein (i.e., an

antibody) that contains a chemically reactive group (i.e., a sulfhydryl) and a ligand (i.e., an antigen) as outlined in the original rejection. Furthermore, Ganem et al discloses both examples wherein the mass spectrometer detects both "covalent" and "non-covalent" interactions and specifically point out that this method is particularly valuable for antibody-antigen complexes that would include those antibody-antigen complexes of Pitner et al.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

13. Claims 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**) and Loo, J. A. (Loo, J. A. "Studying Noncovalent Protein Complexes by Electrospray Ionization Mass Spectrometry" *Mass Spectrometry Reviews*, **1997**, *16*, 1-23).

For **claims 58**, Pitner et al (see entire document) teaches [a] a method for identifying a ligand less than 2000 daltons in size (see Pitner et al, figures 6-7, see also column 4, paragraph 5, see also Examples 1-9, showing PC ligands that are ~250 Da), [b] that bind to a chemically reactive group (see Pitner et al, figure 1, showing chemically reactive group could be either SH or NH, see also column 3 lines 49-58), [c] at a site of interest on the target protein (see Pitner et al, figure 1, disclosing the "antigen binding site" as the "target of interest", see also column 3, paragraph 1), [d] to form a target protein-ligand conjugate (see Pitner et al, figure 1, see also figures 6-7, see also Examples 1-9).

For **claims 59-61**, Pitner et al discloses PC ligands that are ~250 Da (see Pitner et al, entire document, especially figures 1, 6-7 and Examples 1-12).

The prior art teachings of Pitner et al differ from the claimed invention as follows:

For **claims 58**, Pitner et al is deficient in that it does not specifically teach the use of "mass spectrometry" for detecting the protein-ligand conjugate. Pitner et al would require the "identification" of "modified" antigens like PC-MAL that possess a stronger binding affinity to antibodies like SH-McPC603 than the normal PC ligand (see Pitner et al, figures 3 and 7) using an analytical technique like mass spectrometry.

However, Loo teaches the following limitations that Pitner et al lacks:

For **claim 58**, Loo teaches the use of mass spectroscopy for the "identification of novel protein-ligand interactions" including "antibody-antigen" conjugates (see Loo, entire document, especially page 14, section VI, paragraph 2, see also page 2, paragraph 1; see also abstract).

It would have been obvious to one skilled in the art at the time the invention was made to "identify" antibody/antigen interactions using the method steps as taught by Pitner et al in conjunction with the mass spectrometer techniques for the "identification of novel protein-ligand interactions" as taught by Loo because Loo explicitly states that the mass spectrometry can be applied to a broad range of protein-ligand interactions including "antibody-antigen" complexes (see Loo, page 2, paragraph 1), which would encompass the "antibody-antigen" complexes of Pitner et al. Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Loo with the antibody-antigen conjugates as taught by Pitner et al because Loo

explicitly states that mass spectroscopy offers many advantages including speed, sensitivity, stoichiometry and mass accuracy (see Loo, abstract, see also page 4, column 1) for analyzing the protein/ligand interactions and their binding affinities.

Finally, one of ordinary skill in the art would have reasonably expected to be successful because Loo shows many examples of protein-ligand interactions that have successfully been analyzed on a mass spectrometer (e.g., see Table I). Furthermore, the reference explicitly states that it can be successfully applied to antibody-antigen interactions (see Loo, page 2, paragraph 1).

Response

14. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue **[1]** that there is no motivation to combine "just as in the previous rejection" i.e., there is no motivation to search for antigens in an antibody-antigen complex because they are already "known" (see Paper No. 10, page 12, paragraph 4) and **[2]** even if a person of skill in the art were inclined to identify known ligands they would not turn to Loo because Loo deals with a completely different problem i.e., "non-covalent" interactions.

This is not found persuasive for the following reasons:

The Examiner contends **[1]** that all of the antigens are NOT known and there would be motivation to search for "modified" antigens like PC-MAL that possess a stronger binding affinity to antibodies like SH-McPC603 than the normal PC ligand using mass spectrometry (see Pitner et al, figures 3 and 7).

Furthermore, the Examiner contends that it would have been obvious to one skilled in the art at the time the invention was made to combine the references of Pitner et al and Loo for the reasons of record which state that Loo explicitly teaches the use of mass spectrometry with a broad range of protein-ligand interactions including "antibody-antigen" complexes (see Loo, page 2, paragraph 1), which would encompass the "antibody-antigen" complexes of Pitner et al. In addition, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Loo with the antibody-antigen conjugates as taught by Pitner et al because Loo explicitly states that mass spectroscopy offers many advantages including speed, sensitivity, stoichiometry and mass accuracy (see Loo, abstract, see also page 4, column 1) for analyzing the protein/ligand interactions and their binding affinities (Please note that Applicants did not address this issue in the previous action).

The Examiner also contends that **[2]** Loo does teach that both "covalent" and "non-covalent" interactions can be analyzed with a mass spectrometer and explicitly states that the mass spectrometry can be applied to a broad range of protein-ligand interactions including "antibody-antigen" complexes (see Loo, page 2, paragraph 1), which would encompass the "antibody-antigen" complexes of Pitner et al.

For example, Loo teaches both "covalent" and "non-covalent" interactions and explicitly states that it can be used for antibody-antigen complexes like the ones used in Pitner et al (see

Loo, page 2, paragraph 1). For example, Loo et al discloses a peak at 1972 for the "non-covalent" complex of (SRC with Ac-QpYEEIP-NH2)$^{7+}$ and also another peak at 1614 for the uncomplexed SRC (SRC)$^{8+}$ (see Loo et al, page 11, figure 4). The 1972 peak clearly demonstrates that mass spectroscopy can be used to identify "non-covalent" complexes because the 1972 peak represents the molecular weight of Src complexed non-covalently to Ac-QpYEEIP-NH_2. However, the spectrum further shows a peak at 1614 for the un-complexed Src, which contains many "covalent" bonds (e.g., Src is a protein which has many "covalent" bonds such as the covalent bonds that connect the peptide backbone or the amino acid side chains). Consequently, it would be immediately obvious to a person of skill in the art that "covalent" bonds do NOT interfere with experiment (i.e., the fact that Src has "covalent" bonds does not render it undetectable in a mass spectrometer). Therefore, Loo does not teach a "completely different problem" than Pitner et al as purported by Applicants because the physical distinction between "covalent" and "non-covalent" interactions as applied to mass spectroscopy is of no practical consequence (as shown above). A person of skill in the art would have been motivated to combine Pitner et al with Loo et al because Loo et al explicitly states that mass spectrometry can be used for antibody-antigen complexes like the ones disclosed by Pitner et al (see Loo et al, page 6294, paragraph 1) whether they are of a "covalent" nature or not.

Furthermore, as stated above a person of skill in the art would be motivated to use mass spectroscopy precisely because it does detect BOTH "covalent" and "non-covalent" bonds and, as a result, could help distinguish between modified antibodies that are binding to their antigens via the desired "covalent" bonds versus any unwanted "non-covalent" interactions that might

occur through conformational changes to the antibody upon modification (e.g., with a sulfhydryl group).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Double Patenting

15. The terminal disclaimer filed on April 18, 2003 disclaiming the terminal portion of any patent granted on this application that would extend beyond the expiration date of U.S. Patent No. 6,335,155, and any patent granted on U.S. Patent Application Publication Nos. 2002/0081621 A1, 2002/0155505 A1, 2002/0022233 A1, and 2003/0013125 A1 has been reviewed and is accepted. The terminal disclaimer has been recorded.

New Rejections

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 58, 59 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Przybylski et al (IDS reference, Paper No. 11).

For ***claims 58, 59 and 61***, Przybylski et al (see entire document) discloses a method of identifying a ligand that is less than 750 daltons in size (1,2-cyclohexanedione MW = 112 Daltons), that binds to a chemically reactive group (arginine) at a site of interest (places where arginine residues have intramolecular proton acceptor residues in their microenvironment) on a target protein (lysozyme) to form a target-protein ligand conjugate (N^7,N^8-(dihydroxycyclohexanediyne) addicts) by mass spectrometry (ESI-MS) (see Przybylski et al, paragraph bridging pages 811-812 and figure 5), which anticipates claim 58, 59 and 61. Please note that even though the ligand disclosed by Przybylski et al (i.e., 1,2-cyclohexanedione) was "known" before its addition to the target protein, it was "not known" whether said ligand would bind to a particular site of interest or not and, as a result, it still has to be "identified" as a ligand that binds to a site of interest (i.e., 1,2-cyclohexanedione was "identified as a ligand that binds to sites of interest" in a lysozyme using ESI-MS).

Conclusion

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on April 18, 2003 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D. Epperson, Ph.D. whose telephone number is (703) 308-2423. The examiner can normally be reached on Monday-Thursday from 9:30 to 7:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon D. Epperson, Ph.D.
June 28, 2003

BENNETT CELSA
PRIMARY EXAMINER